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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/047,652	03/25/1998	VASSILIOS PAPADOPOULOS	009/064/SAP	3470

909 7590 01/28/2004

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/28/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/047,652	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-68* is/are pending in the application.

4a) Of the above claim(s) *58-63 and 66-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-57,64 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request filed on 01/06/03 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No:09/407652 is acceptable and a CPA has been established. An action on the CPA follows.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 53-68 are pending. Claims 58-63, 66-68 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Claims 53-57, 64-65 are being examined.

The following are the remaining rejections.

OBJECTION

1. Claim 53 is objected for the use of the grammatically incorrect language are having....This objection could be obviated if Applicant amends the claim for example to delete the language "are".

For the purpose of compact prosecution, it is assumed that claim 53 is drawn to an antisense oligonucleotide that has a structure complementary to at least a portion of the peripheral-type benzodiazepine receptor (PBR) having the nucleic acid sequence contained in SEQ ID NO:1 or 2, wherein said antisense oligonucleotide inhibits the expression of PBR gene in a cell line that expresses PBR gene, and thereby inhibits proliferation of said cell line.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

1. Claims 53-57, 64-65 remain rejected under 35 U.S.C. 112, first paragraph, pertaining to lack of enablement for an antisense oligonucleotide that inhibits the expression of PBR gene in a cell line that expresses PBR gene, and thereby inhibits proliferation of said cell line, for reasons already of record in paper No: 18.

Claims 53-57, 64-64 are drawn to an antisense oligonucleotide that has a structure complementary to at least a portion of the peripheral-type benzodiazepine receptor (PBR) having the nucleic acid sequence contained in SEQ ID NO:1 or 2, wherein said antisense oligonucleotide inhibits the expression of PBR gene in a cell line that expresses PBR gene, and thereby inhibits proliferation of said cell line. Said antisense oligonucleotide possesses a size ranging form 7 to 40 nucleotides. Said cell line could be a human breast cancer cell line. Said antisense oligonucleotide is comprised in a vector which is expressed in the mammary gland.

The specification discloses that SEQ ID NO:1 and 2 are partial cDNA sequences of PBR identified in breast cancer cell lines MDA-231 and MCF-7, respectively (p.15), wherein the breast cancer cell line MDA-231 is more aggressive, and expresses PBR at higher level than the non-aggressive cell line MCF-7 (page 36 and table 1 on page 36). The specification further discloses that the region surrounding the translation site and 5' to the translation has not yet been obtained (p.16, lines 7-10). In other words, the size of the overexpressed full length PBR mRNA in MDA-231 and MCF-7 is not necessarily the same size as the isolated partial sequence corresponding to SEQ ID NO:1 or 2. Under MPSRCH sequence similarity search, SEQ ID NO:1 and 2, both consist of 652

nucleotides as compared to a total 821 nucleotides of the full length human PBR taught by Riond et al, Eur J Biochem, 195(2): 305-311 (MPSRCH search report, 1998, us-09-047-652A-1.rge, p.1-2, and us-09-047-652A-2.rge, p.1-2, respectively).

The specification also discloses that by homologous recombination of wild type PBR in rat Leydig tumor cell line, using as a vector for recombination, a PBR fragment spanning the exon 2, intron 2 and the first 42 bp of exon 3, which is connected via a neo expression cassette to a second PBR fragment spanning 117 bp of exon 3, intron 3, and the first 270 bp of exon 4, one allele of PBR gene is inactivated, resulting in suppression of mRNA expression of PBR and reduced cell growth (Example 7, on pages 45-46, and the recited reference by Papadopoulous, 1997, JBC, 272: 32129-32135).

One cannot extrapolate the teaching in the specification to the enablement of the claims.

It is noted that a complement could be a full length or partial complement, wherein a partial complement could share or comprise only a few nucleotides of SEQ ID NO:1 or 2. It is further noted that a portion could encompass one or two nucleotides. Thus the claims encompass antisense oligonucleotides with unknown structure, which share with SEQ ID NO:1 or 2 only a few complementary nucleotides.

The specification however does not disclose how to make such antisense oligonucleotide variants such that they would function as claimed. In view of a lack of such a teaching, one would not know how to make the claimed antisense oligonucleotide variants such that they would inhibit expression of PBR.

Further, one cannot correlate the example on homologous recombination in rat Leydig tumor cell line with the enablement of the claims, because in Example 7, one whole allele of PBR gene is inactivated, and PBR mRNA is absent (Papadopoulos, V, supra, p. 32132, second column, last 7lines of paragraph before last). It is not predictable which sites on the whole length PBR sequence is responsible for inactivation of the expression of the PBR gene, and whether these sites would be contained within the partial cDNA sequences of SEQ ID No:1 or 2, in view of the teaching of US 5,585,479 (of record) that active antisense sequences could not be predicted. US Patent No. 5,585,479 discloses an effective oligonucleotide and show that moving the target just one or two bases, can greatly reduce or even eliminate, antisense activity (data disclosed in columns 15-17). US Patent No. 5,585,479 states that "there are no rational explanations or rules that would predict active sequences". The specification however does not disclose which antisense oligonucleotides within the claimed partial cDNA sequence of SEQ ID NO:1 or 2, that would be expected to function as an effective antisense binding site. Thus, in view of the unpredictability of whether there exist antisense molecules within the claimed partial cDNA sequence of SEQ ID NO:1 or 2 that would function effectively to inhibit PBR gene expression, and in the absence of evidence to the contrary, a skilled artisan would be unable to practice the claimed invention using the claimed antisense sequences without undue experimentation and with a reasonable expectation of success.

2. Claim 65 remains rejected under 35 USC pertaining to lack of enablement for the claimed antisense oligonucleotide that is expressed in the mammary gland in vivo as

contemplated, wherein said antisense oligonucleotide inhibits the expression of PBR gene, for the same reasons already of record in paper No:18. Claim 64 is rejected for the same reasons of record.

Claim 64 is drawn to an antisense oligonucleotide, that has a structure complementary to a portion of the nucleic acid sequence contained in SEQ ID NO:1 or 2, wherein said antisense oligonucleotide inhibits the expression of PBR gene in a cell line that expresses PBR gene, and thereby inhibits proliferation of said cell line, and wherein said antisense oligonucleotide is comprised in a vector.

Claim 65 is drawn to an antisense oligonucleotide, that has a structure complementary to a portion of the nucleic acid sequence contained in SEQ ID NO:1 or 2, wherein said antisense oligonucleotide inhibits the expression of PBR gene in a cell line that expresses PBR gene, and thereby inhibits proliferation of said cell line, and wherein said antisense oligonucleotide is comprised in a vector which is expressed in the mammary gland.

Applicant argues that it is predictable that the sequences can be selected which will be effective, based on the information in the disclosure (Example 7) that inhibition of the expression of one allele of the PBR gene resulted in the reduction in cell proliferation of a cancer cell line. Applicant further argues that SEQ ID NO:1 and 2 which are partial cDNA sequences of PBR are identified in breast cancer cell lines MDA-231 and MCF-7, respectively (p.15), wherein the breast cancer cell line MDA-231 is aggressive. Applicant asserts that the expression of these sequences may represent an early event in the progression of the disease. Applicant further asserts that nuclear

PBR is responsible for regulating the movement of cholesterol into nuclear membrane, and that this regulation is related to the modulation of cell proliferation.

Applicant's arguments set forth in paper No.15 have been considered but are not deemed to be persuasive for the following reasons:

The specification discloses that agents that decrease the level of PBR may be used in the therapy of any disease associated with the elevated levels of PBR such as metastatic cancer, e.g. breast cancer (p.25, last paragraph). The specification discloses that agents that decrease the level of PBR include antisense oligonucleotides capable of hybridizing to PBR RNA such that the translation of PBR is inhibited or reduced. The specification discloses that these antisense oligonucleotides can be administered as part of a vector which can be expressed in the target cell. The specification discloses that vector that are expressed in particular cell types, e.g. mammary gland, are known in the art (p. 26, lines 3-19).

Claim 64 encompasses an antisense oligonucleotide in a vector, for expression in vivo, as contemplated, that has a structure complementary to a portion of the nucleic acid sequence contained in SEQ ID NO:1 or 2.

Claim 65 encompasses an antisense oligonucleotide expressed in vivo in the mammary gland, as contemplated, that has a structure complementary to a portion of the nucleic acid sequence contained in SEQ ID NO:1 or 2.

One cannot correlate the example on homologous recombination in rat Leydig tumor cell line, with the claims, because in said example, one whole allele of PBR gene is inactivated, and it is not predictable which sites on the whole length PBR sequence is

responsible for inactivation of the expression of the PBR gene, and whether these sites would be contained in the partial cDNA sequences of SEQ ID No:1 or 2, *supra*. Further, it is unpredictable that said antisense oligonucleotide could be successfully used *in vivo*, because 1) successful application of antisense therapy *in vivo* has been extremely limited, and 2) even if the biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss (of record). Similarly, Branch, AD, 1998 (of record) teaches that it is very difficult to predict what portions of an RNA molecule will be accessible to an antisense sequence *in vivo*, and therefore, rational design of antisense molecule is not possible. In addition, Branch also teaches that although some antisense molecules had some clinical value through non-antisense effects, the non-antisense effects are not predictable and these effects must be explored on a case-by-case basis (p50, first column).

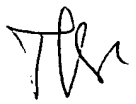
Thus given the unpredictability of the behavior and effect of antisense oligonucleotide in vivo, it is unpredictable that the claimed antisense oligonucleotide would inhibit or reduce the expression of PBR in vivo in mammary gland, and thus one would not know how the use the claimed antisense oligonucleotides for in vivo expression as contemplated.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 703-308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.



MINH TAM DAVIS

PATENT EXAMINER

January 21, 2003